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Temporal Trends in the Risks of Stroke and Death due to Endarterectomy for Symptomatic Carotid Stenosis: An Updated Systematic Review

K. Rerkasem [a], **P.M. Rothwell** [b,*]

[a] *Vascular Surgery Division, Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*
[b] *Stroke Prevention Research Unit, University Department of Clinical Neurology, John Radcliffe Hospital, Oxford, UK*

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Abstract *Objectives:* To determine whether there is any evidence of a systematic reduction in the operative risk of carotid endarterectomy (CEA) for symptomatic stenosis in recent years.
Methods: We performed a systematic review of all studies published between 2000 and 2008 inclusive that reported the risks of stroke and death for symptomatic carotid stenosis. We compared the reported risks with our previous review of studies published prior to 2001 and between studies that were reported by surgeons alone and studies that included neurologists or stroke physicians as assessors/authors, with particular reference to the proportion of operative strokes to operative deaths.
Results: Of 494 studies, only 53 reported operative risks for patients with symptomatic stenosis separately. In keeping with the findings of our previous review, the pooled operative risk of stroke and death reported in studies published by surgeons alone (3.9%, 95% confidence interval (CI): 3.4–4.3) was significantly lower ($p < 0.001$) than that reported in studies that involved neurologists (5.6%, 95% CI: 5.1–6.2). The pooled ratio of operative stroke:operative death was 4.0 (range: 3.6–4.5) in studies involving neurologists or stroke physicians and 2.7 (range: 2.1–3.9) in studies involving only surgeons ($p = 0.002$). We found no evidence of a reduction in published risks of death or stroke and death due to CEA for symptomatic carotid stenosis between 1985 and 2008. Indeed, the 1.4% (range: 1.2–1.6%) pooled operative mortality in studies published during 2001–2008 was significantly higher than that reported in ECST and NASCET (1.0%, 95% CI: 0.9–1.1%). However, the average age of patients having CEA has continued to increase during this period.

* Corresponding author. Tel.: +44 (0) 1865231603; fax: +44 (0) 1865234639.
E-mail address: peter.rothwell@clneuro.ox.ac.uk (P.M. Rothwell).

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Conclusions: There is no evidence of a systematic reduction over the last decade in the published risks due to CEA for symptomatic stenosis. The lower proportion of non-fatal operative strokes in surgeon-only studies suggests that some minor operative strokes have been missed.
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It has been shown in large randomised trials that carotid endarterectomy (CEA) reduces the risk of stroke in patients with recently symptomatic ≥70% stenosis and is of some benefit in selected patients with recently symptomatic 50–69% stenosis.[1–3] Benefit depends on maintaining a low operative risk of stroke and death. Some surgeons now operate on low-risk patients with 50–69% stenosis, believing that improved surgical techniques make current operative risks significantly lower than the 7% risk of stroke and death reported in the major trials performed in the late 1980s and early 1990s.[4,5] This belief is supported by more recent reports of operative risk of stroke and death of 2–3%.[5,6] However, low operative risks were also reported in the 1980s.[7,8] Moreover, there have also been significant improvements in the medical management of carotid disease in recent years, which might reduce the absolute benefit of CEA even if the operative risk has fallen. Before proposing any broadening of the indications for surgery over and above those from the randomised trials, it is important to establish whether there is any evidence of a systematic reduction of surgical risk in recent years.

Assessment of the absolute risk of stroke and death from CEA in routine clinical practice is difficult. Large studies of data routinely collected are least likely to have selection or publication bias.[9,10] However, these studies often only report data on operative mortality and do not usually differentiate CEA for symptomatic stenosis from CEA for asymptomatic stenosis. The risks of stroke and death in published case series are very heterogeneous, partly because of differences in how outcome was assessed[11] and partly because of differences in case mix.[7,12,13] However, if analyses of time trends are stratified according to such factors, it is possible to determine by studying published reports whether operative risks have fallen significantly in recent years. We therefore systematically reviewed all studies on the outcome of CEA for symptomatic carotid stenosis published from 2001 to 2008 and compared the operative risks with those from the ECST and NASCET[1,2] and our previous review of earlier studies.[7,8,14] Most studies published before 2000 recruited patients during the same period as the large trials, but most studies published after 2000 recruited patients after the trials stopped randomising patients with severe stenosis in 1991.[15,16]

Methods

We updated our previous review by systematically reviewing all published papers reporting outcome of CEA from 1 January 2001 to 31 August 2008. We re-searched 2000 again. Although our previous review covered the period up to and including 2000, there is a delay between publication of papers and inclusion in bibliographic databases, so we could have missed some papers published towards the end of our previous review period.

Search strategy

The literature search for our previous review was done by two independent researchers with a high degree of agreement (>90%)[14] in identification of eligible studies. The current search for this updated review was therefore performed by one researcher only (KR).

1) Studies were identified from Medline and Embase with 'carotid endarterectomy' as the search term. Animal studies, studies with results of carotid surgery for non-atherosclerotic disease and review articles with no original data were excluded by reading the titles or the abstract and full paper where necessary. The reviewer then searched the resulting list of references for any reports that might contain relevant information. These were then pooled, and the process was repeated, using either the abstract and/or the full report to establish relevance (Fig. 1).
2) The bibliographies of all papers identified electronically were also searched.
3) The six journals with the largest number of relevant papers were searched manually for the period 2000–2008 (Fig. 1).

Inclusion criteria

Papers published in any language were included if they fulfilled the following criteria:

1) The numbers of combined strokes and deaths occurring within 30 days of CEA (or a similar time period) were reported.
2) The risks of stroke and/or death were defined, or able to be calculated, per operation.
3) Operative risks were reported by clinical indication. As a minimum, operative risks for symptomatic and asymptomatic stenosis were reported separately.
4) Patients with bilateral simultaneous endarterectomy were excluded, or data were reported separately so that they could be excluded from the analysis.
5) Patients with synchronous endarterectomy and coronary artery bypass grafting were excluded, or data were reported separately so that they could be excluded from the analysis.

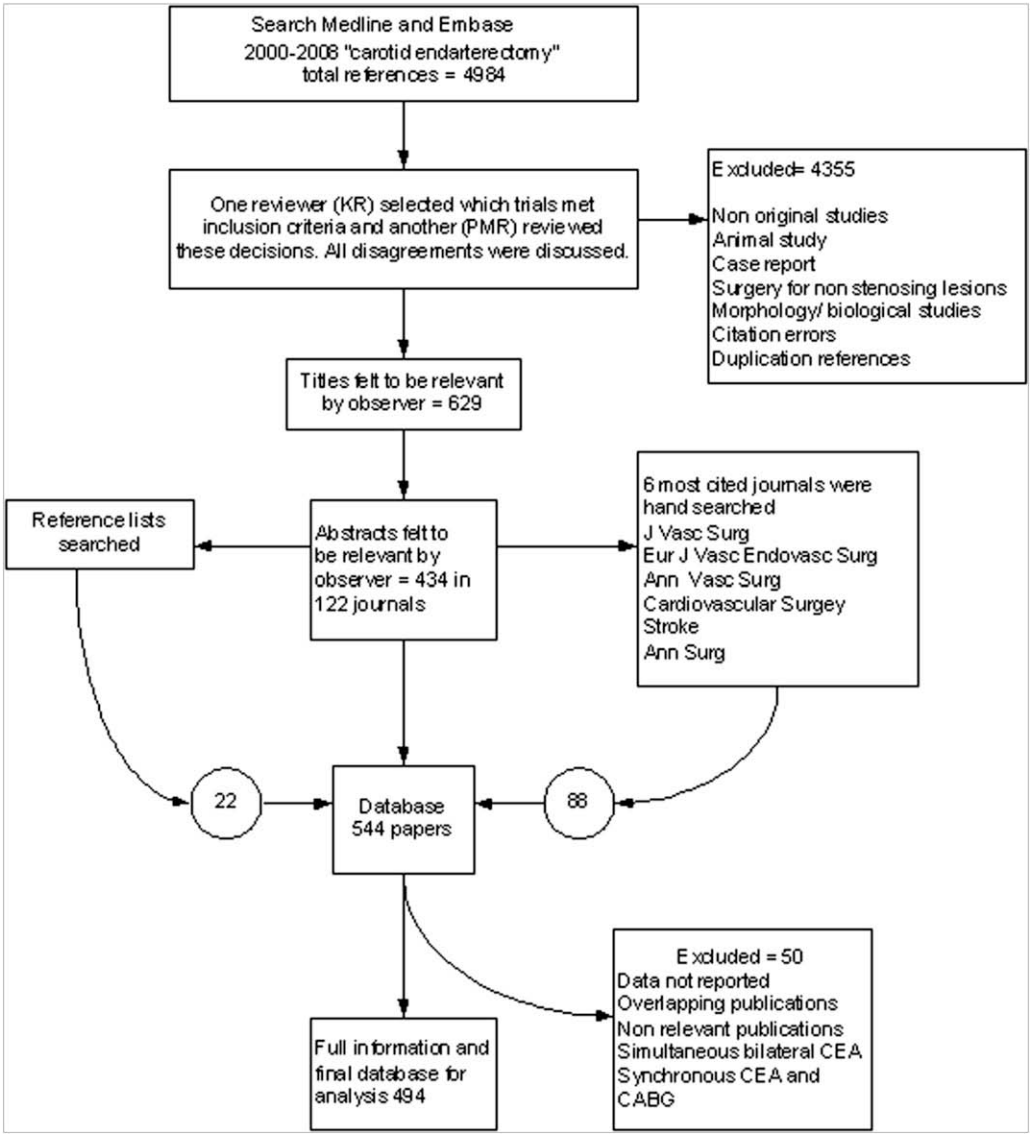

Figure 1 Strategy and results of the literature search.

Extraction of data

One researcher (KR) reviewed each article and recorded the number of operations performed, the number of patients undergoing surgery and the number of strokes and deaths during the operative and postoperative periods. Another researcher (PMR) reviewed the data. All disagreements were re-examined jointly and corrections made when necessary. To locate duplicate reporting of the same cohort of patients, the authorship of all papers was cross-referenced. When duplication was thought likely, only one paper (usually the paper reporting the larger cohort) was included. After exclusion of duplicates or articles with inadequate data, a final database of articles was compiled for analysis.

Analysis

Mantel—Haenszel meta-analysis was used to calculate pooled estimates of operative risk. Allowance was made for extra-binomial variation when calculating the 95% confidence intervals (CIs) of the pooled risk estimates[17] since standard methods of calculating CIs result in artificially narrow intervals when there is heterogeneity of risk in different studies. To study time trends of operative risk, the authors combined our results with those from our previous review of studies published before 2000.[7,8,14]

The pooled analyses of operative risk of stroke and death were stratified according to whether one or more authors were affiliated to a department of neurology or medicine, even if it was not explicitly stated who had assessed the outcome. We also calculated the ratio of all operative strokes to operative deaths (an indirect measure of the severity of operative strokes — the proportion of non-fatal strokes) and obtained pooled estimates for studies including neurologist or stroke physician authors versus studies with surgeon authors only.

Results

The results of the literature search are in Fig. 1. A total of 4984 references were found by electronic search; of these, 4355 were excluded by reading the titles, since they were clearly review articles, animal studies or reports of non-endarterectomy carotid surgery. After a review of the abstracts, the remaining 629 references were reduced to 434. In addition, 22 papers were found from the reference lists of these 434 papers, and an additional 88 papers were found by a manual search of the six journals that furnished most papers in the electronic search for the period 2000–2008 (Fig. 1). There were 22 papers that had been published during 1995–2000 but had not been identified and included in the previous review.

After excluding duplicates or articles with inadequate data, a final database was compiled of 494 articles, published in 2000–2008, relating to the risk of stroke and death following CEA. Of these, 164 reported the outcome of surgery but had no information about the indication, and 256 reported the proportion of symptomatic versus asymptomatic patients operated upon but did not report the operative risk separately. Of the remaining 74 studies, 53 reported data on the operative risks of stroke and death rate following CEA for symptomatic carotid stenosis. An additional 103 studies were included from our previous review covering the period before 2001.

The overall pooled estimate of the operative risk of stroke and death reported in studies published from 2001 to 2008 was 4.9% (95% CI: 4.3–5.3). However, as in the previous review,[7,8,14] the operative risk in studies published by surgeons only (3.9%, 3.4–4.3%, 25 studies) was significantly lower ($p = 0.002$) than that in studies with some involvement of neurologists or stroke physicians (5.6%, 5.1–6.2%, 21 studies). The risks in studies that involved neurologists or stroke physicians were similar to those in the ECST and NASCET combined (7.0%, 6.2–8.0%). There was significant heterogeneity in the risks of stroke and death within both groups of studies (Fig. 2), but 14 of the 21 studies with a neurologist or stroke physician had higher risks than the 3.9% pooled estimate from the surgeon-only studies (Fig. 3). Furthermore, the pooled estimate of risk of stroke and death in the neurologist or stroke physician studies was still higher than that in the surgeon-only studies when the analysis was restricted to non-trial case series (5.6%, 5.1–6.2%, 16 studies) by exclusion of data from the Wallstent,[18] Kentucky,[19] EVA-3S,[20] SPACE[21] and BACASS trials.[22]

The overall risk of operative death in the 34 studies that reported operative mortality separately for symptomatic patients from 2001 to 2008 was 1.4% (95% CI: 1.2–1.6). This operative mortality was greater than that reported in ECST and NASCET (1.0%, 95% CI: 0.9–1.1). However, there was no statistically significant difference in operative mortality between surgeon-only studies (1.1%, 95% CI: 0.7–1.6, 19 studies) and studies with a neurologist or stroke physician (1.5%, 95% CI: 1.3–1.7, 15 studies). The pooled ratio of operative stroke to operative death was 4.0 (3.6–4.5) in studies with neurologists or stroke physicians and 2.7 (2.1–3.9) in studies with surgeons only ($p < 0.001$). The lower proportion of non-fatal operative strokes in surgeon-only studies suggests that some minor operative strokes were missed.

The time trends in operative risk are detailed in Table 1 and Fig. 4. Although at first there was a significant reduction in stroke and death rates published up to 1980, there has been no statistically significant change over the last 25 years (Fig. 4). Throughout this period, published risks from studies with a neurologist or stroke physician have been consistently higher than those in surgeon-only studies (Table 1). This difference was most pronounced in the small number of early studies.

The average age of patients operated on has gradually increased from 60.9 years in studies prior to 1980 to 70.3 years in studies from 2000 to 2008 ($p < 0.00001$, Fig. 4). However, the sex ratio has not changed significantly; 32.3% of operations were done on women from 2000 to 2008.

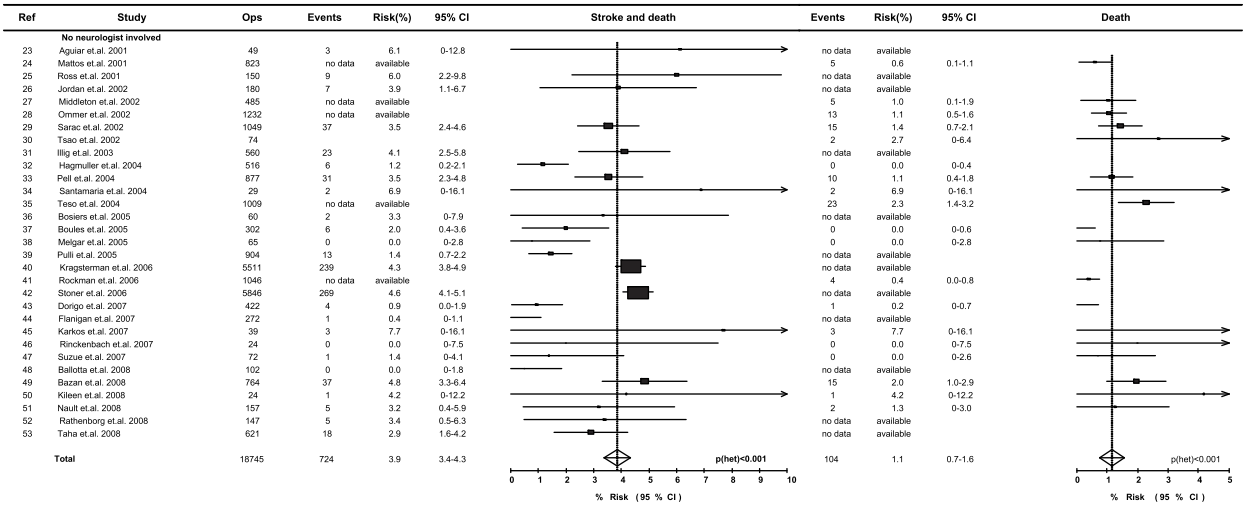

Figure 2 Meta-analysis of operative death rates and combined stroke and death rates following carotid endarterectomy in symptomatic patients in studies with authorship by surgeons only, published during 2001–2008. p(het) is the statistical significance of the heterogeneity of odds ratios across studies.[23-53]

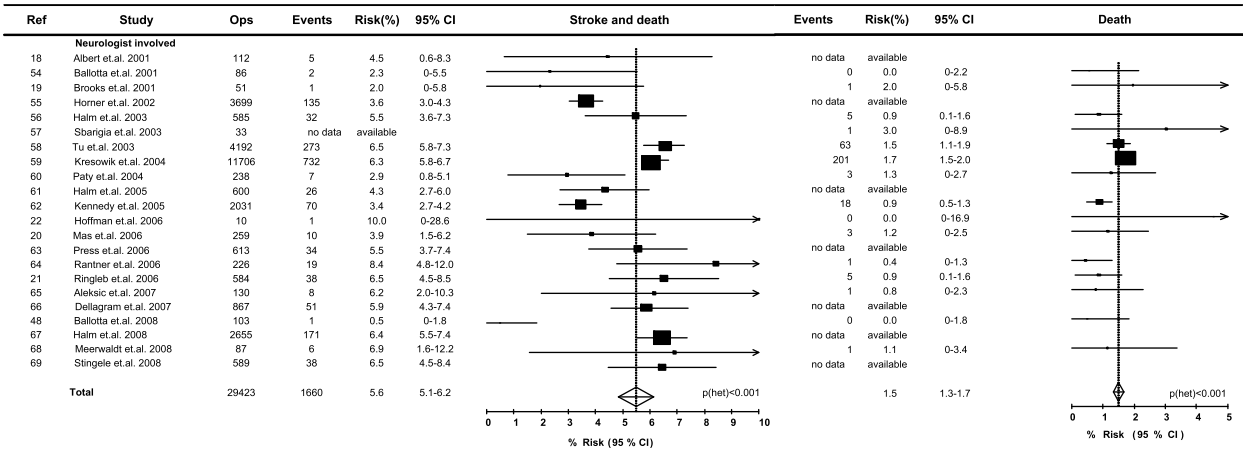

Figure 3 Meta-analysis of operative death rates and combined stroke and death rates following carotid endarterectomy in symptomatic patients in studies with authorship including a neurologist or stroke physician, published during 2001–2008. *p*(het) is the statistical significance of the heterogeneity of odds ratios across studies.[18-22,48,54-69]

Discussion

We attempted to review all of the published literature on the operative risk of death and stroke due to CEA for symptomatic stenosis. However, electronic searches inevitably miss some published studies, and it was impossible to search every journal manually. However, it is unlikely that there was a systematic bias of inclusion of studies with respect to reported mortality or morbidity. Complete ascertainment of reports is vital in systematic reviews of randomised controlled trials because 'negative' trials are more likely to be published in low-profile journals and to therefore be missed. The potential biases due to under-ascertainment of surgical case series are likely to be

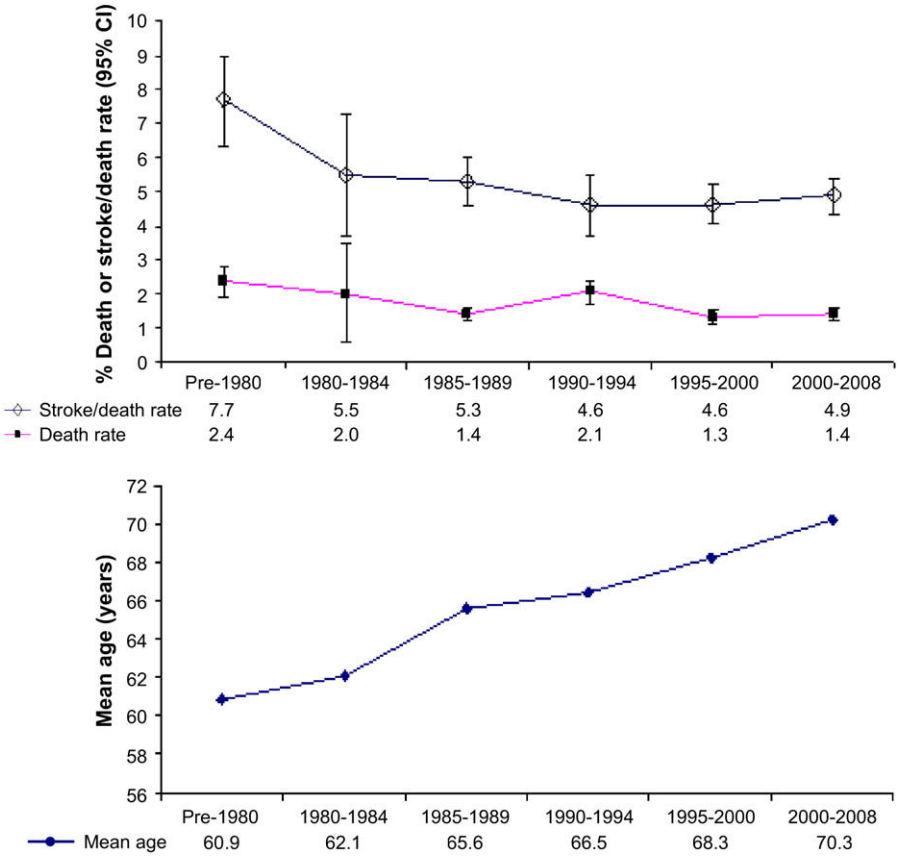

Figure 4 Time trends in studies of carotid endarterectomy for symptomatic stenosis published between 1980 and 2008 for: operative death rates and stroke and death rates (above) and average age of patients operated upon (below).

Table 1 Time trends of the risk of stroke and death and operative mortality from carotid endarterectomy in symptomatic patients stratified by authorship for studies published during 1980—2008.

	Neurologist or Physician			Surgeon only		
	N	Stroke and death (95% CI)	Death (95% CI)	*N*	Stroke and death (95% CI)	Death (95% CI)
Year published						
Pre 1980	4	18.3 (12.2—24.4)	6 (2.1—11.2)	3	4.7 (2.4—7.0)	3.1 (0.8—5.4)
1980—1984	7	13.2 (7.6—18.8)	4.3 (0.0—8.8)	9	4.1 (2.9—5.3)	1.6 (0.9—2.3)
1985—1989	3	6.4 (4.6—8.2)	5 (1.4—1.7)	14	5.0 (4.0—6.0)	1.4 (1.1—1.7)
1990—1993	6	6.5 (5.4—7.6)	2.9 (0.3—5.5)	12	4.6 (3.6—5.6)	1.9 (1.3—2.4)
1994—2000	11	6.5 (4.3—8.7)	1.6 (1.3—2.0)	34	4.2 (3.5—4.9)	1.4 (1.2—1.6)
2001—2008	21	5.6 (5.1—6.2)	1.5 (1.3—1.7)	25	3.9 (3.4—4.3)	1.1 (0.7—1.6)

smaller. Similarly, only 10.7% (53 of 494) of the studies published from 2001 to 2008 fulfilled our inclusion criteria, the vast majority of studies being excluded simply because the risks of CEA were not reported separately for patients undergoing surgery for symptomatic and asymptomatic stenosis. Since the risks of surgery for asymptomatic stenosis are consistently lower than those for symptomatic stenosis,[7,14] combined risks would have been difficult to interpret. These exclusions were unavoidable and were also unlikely to have introduced substantial bias. Most importantly, the same methodology was applied in our previous review and therefore any effects of study selection should not have biased our assessment of time trends.

The risks of stroke and death reported were statistically significantly heterogeneous between studies. Differences between studies may be attributable to differences in case mix or surgical experience, but the analysis suggests that differences in study methodology account for some of the heterogeneity. As in the previous review,[8,14] studies with some involvement of a neurologist or stroke physician had risks of stroke and death higher than those in studies with surgeons only. Potential reasons for this disparity have already been discussed.[11,70] In brief, it is likely that publication bias explains some of the difference. Surgeons with high operative risks may not be inclined to publish results. It is more likely that neurologists will audit operative risks if they are high. Another explanation is diagnostic bias: neurologists are more likely to identify minor strokes. This latter explanation is supported by analysis of the proportion of operative strokes that were fatal, or the ratio of non-fatal operative stroke to operative mortality. In NASCET[15] and ECST,[16] this ratio was 6 and 8, respectively. It is likely that studies with much lower ratios have missed some non-fatal strokes. Figs. 2 and 3 show that 39% of surgeon-only studies had ratios of 2 or less compared to only 6% of studies with a neurologist or stroke physician. Irrespective of the reasons, the results here support the previous recommendation that a neurologist should audit the operative risk of CEA.[11]

Many surgeons feel that the outcome of surgery has improved over time because of better quality control and better patient selection. However, although it may be possible to show that results are improving in some centres, there is less evidence of widespread changes. The 5.6% overall risk of stroke or death from CEA in studies from 2001 to 2008 with some involvement of a neurologist or stroke physician is very consistent with the operative risks reported in ECST and NASCET,[15,16] the American Heart Association guidelines[12,13,71] and the earlier review.[7,8,14]

Importantly, the overall pooled 1.4% risk of operative death in studies published during 2001—2008 is statistically significantly higher than the 1.0% risk reported in ECST and NASCET. This difference might be explained partially by differences in case mix, particularly the exclusion, mainly from NASCET, of various categories of patients with a high operative risk.[15] However, the relatively high operative mortality in published case series highlights the importance of appropriate patient selection and fully informed consent.

In conclusion, we have found no evidence that the operative risks of CEA for symptomatic stenosis has fallen over the last two decades. In published case series and trials, risks of both operative mortality and stroke and death have remained stable, although the age of patients has progressively increased. It is difficult to reliably interpret temporal trends in published risks, given the changes in the frequency of operations over the past 25 years and probable changes in the types of patients undergoing surgery. However, claims that operative risks have fallen to such levels that the results of the ECST and NASCET no longer apply to current clinical practice cannot be substantiated. Indeed, improvements in best medical treatment of patients with carotid artery disease are likely, if anything, to have reduced the absolute benefit of CEA. It is important, therefore, that operative risks continue to be audited.

Conflict of Interest

None.

Acknowledgement

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